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CLINICAL INVESTIGATION

Intraventricular Vancomycin In Pediatric Patients With Cerebrospinal Fluid Shunt Infections

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OBJECTIVES To determine: 1) the range and magnitude of vancomycin trough cerebrospinal fluid (CSF) concentrations following intraventricular (IVT) vancomycin; 2) any correlation between patient demographic and CSF vancomycin concentrations; and 3) eradication and complications rates following IVT vancomycin.

METHODS Medical records of pediatric patients with shunt infection who received IVT vancomycin during a 12 month period were reviewed. Demographic, microbiological data, IVT/intravenous (IV) vancomycin dosing, concomitant antibiotics, CSF and serum vancomycin concentrations, and CSF drainage output were recorded.

RESULTS Seventeen patients ages 4 months to 17 years were hospitalized for shunt infection. *Staphylococcus epidermidis* (n=12) was the predominant organism. Sixteen patients received 10 mg, and one patient received 5 mg of IVT vancomycin for 3–23 days. All but one received concurrent IV vancomycin. The mean maximum trough CSF vancomycin concentration noted for 16 patients who recieved 10 mg of IVT vancomycin was 18.4±21.8 μg/mL (range: between 0.4 to 187.3 μg/mL). All four adolescents ≥25 kg had CSF vancomycin concentrations ≤5 μg/mL, three of four infants/children between 10.1 and 24.9 kg had trough CSF vancomycin concentrations between 10–20 μg/mL, and five of nine infants <10 kg had CSF concentrations >20 μg/mL. All organisms were successfully eradicated. One patient developed chronic eosinophilia presumed related to elevated CSF vancomycin concentrations (187 μg/mL).

CONCLUSIONS –The combination of IVT and IV vancomycin effectively eradicated CSF shunt infections. CSF vancomycin concentrations are highly variable and poorly correlated with age and CSF output. Following a 10 mg IVT vancomycin dose, CSF concentrations appear to be lower in older children and elevated in infants/young children. One infant experienced a complication related to an elevated CSF vancomycin concentration; hence, therapy must be individualized, using CSF trough vancomycin concentrations.

KEYWORDS: intraventricular, shunt infection, vancomycin

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INTRODUCTION

The preferred method for shunting cerebrospinal fluid (CSF) from the ventricles is via a ventriculoperitoneal (VP) or ventriculoatrial (VA) shunt. Infection is a major cause of shunt failure, which places the patient at risk of intellectual impairment, the development of loculated CSF compartments, and death. Although the incidence of post-operative CSF shunt infections varies considerably among centers, ranging from 1% to 39%,[1] most report infection rates of about 5%.[2] The most common causative pathogens include *Staphylococcus epidermidis* and *Staphylococcus aureus*. Recently, the emergence of methicillin-resistant strains of Staphylococcus has made vancomycin the antibiotic of choice for this infection.[3]

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While human data are lacking, animal data suggests that the central nervous system (CNS) lacks an active transport mechanism for vancomycin.[4] Also, researchers have reported that in the presence of meningeal inflammation, vancomycin penetration into the CNS is unreliable.[5] Although therapeutic CSF vancomycin concentrations and successful treatment of shunt infections have been reported following intravenous (IV) vancomycin alone,[6-8] the poor CSF penetration following systemic administration may result in failure to eradicate infection.[7-10] Additionally, the bactericidal and bacteriostatic activities, calculated as the ratios of the minimum bactericidal concentration and minimum inhibitory concentration to the CSF vancomycin concentration, were inadequate after three doses (15 mg/kg q 6 hours) of vancomycin.[11] Therefore, direct instillation of the drug into the CNS may be necessary to achieve CSF concentrations capable of successfully eradicating an organism.[12-16]

The purpose of this retrospective study was to evaluate the treatment and outcomes of patients with culture proven CSF shunt infections who were treated with IV and IVT (intraventricular) vancomycin. The objectives were to determine: 1) the range and magnitude of vancomycin trough CSF concentrations following IVT vancomycin; 2) any correlation between patient demographics and CSF vancomycin concentration; and 3) eradication and complications rates following the administration of IVT vancomycin.

METHODS

In order to identify potential patients, medical record discharge codes for shunt infections and neurosurgery records for patients with shunt infections were reviewed for all admissions between June 1999 and June 2000. Patients were included if they were between 0 and 18 years of age and had a VP or VA culture positive shunt infection that was treated with IVT vancomycin (5 or 10 mg) with or without systemic vancomycin (10–15 mg/kg/dose q 6 hours). The shunt was externalized if the patient had signs of peritonitis, evidence of tunnel track infection, septicemia, cor pulmonale, or if the shunt was malfunctioning.

An aspirate of CSF was obtained from the shunt and gram-stain: WBC with differential count, RBC, protein and glucose were determined. A neurosurgeon administered the IVT vancomycin over <2 minutes into the shunt or via the externalized shunt at a concentration of 5 mg/mL and the shunt was clamped for 1 hour. Depending on the particular neurosurgeon and infectious diseases service recommendations, IV vancomycin at dosages of 10–15 mg/kg/dose q 6 hours (maximum 2 gm/day) was given concurrent with IVT vancomycin. The following day, a CSF sample was collected and analyzed for WBC with differential count, RBC, protein, and glucose, and a trough vancomycin CSF concentration was obtained prior to the next dose. The clinical laboratory of our institution determined

Table 1. Patient Demographics

Patient	Gender	Age (yr)	Weight (kg)	ShuntType	Underlying Pathologies	Organism
1	F	14	61	VP	Spina bifida	SE
2	F	15	67	VP	Spina bifida	SE
3	M	16	117	VP	Paraencephalic cyst	GBS
4	M	6	19	VP	Intracranial tumor	SA
5	M	7	25	VP	Head trauma	SE
6	F	0.42	3.4	VP	Craniosynostosis	SE
7	F	3	12.8	VP	Unknown	SE
8	F	1.66	10	VP	IVH	SE
9	M	4	18	VP	Intracranial tumor	SA
10	F	1.58	10	VP	Aqueduct stenosis	SE
11	F	1.33	9.25	VP	IVH	SE
12	F	17	10	VP	IVH	SE
13	F	0.42	5.5	VP	Unknown	SE
14	M	0.33	3.3	VP	IVH	SE
15	F	4	15	VA	Anoxic brain injury	SE
16	M	0.75	6	VP	Fronto-nasal encephalocele	BS
17	M	0.8	9.6	VP	Congenital hydrocephalus	SA

VP, ventriculo-peritoneal; VA, ventriculo-atrium; IVH, intraventricular hemorrhage;
SE, *Staphylococcus epidermedis;* GBS, *Group B streptococcus;* SA, *Staphylococcus aureus;*
BS, *Bacillus species*

CSF vancomycin concentrations using a fluorescence polarization immunoassay (FPIA-AxSYM, Abbott Laboratories).

Although sterilization of the CSF has been achieved with a variety of CSF vancomycin concentrations, a concentration of 5 μg/mL showed slightly lower activity (not statistically significant) than concentrations of 10, 100, 300 μg/mL,[12] and a concentration of 2 μg/mL was significantly less bactericidal than a concentration of 5 μg/mL.[12] These authors contend that time-dose regimens that provide trough CSF vancomycin concentrations of 5–10 μg/mL provide maximal effectiveness. The above studies are the basis for our neurosurgeons' practice and are the reason we used of a trough CSF vancomycin concentration between 5 and 10 μg/mL in this study.

Each CSF vancomycin concentration was reviewed by the neurosurgeon, and the IVT dosage was adjusted as needed. If the trough vancomycin concentration was <20 μg/mL, the same dose of IVT vancomycin was injected the next day into the shunt or via the externalized shunt. If the concentration was >20 μg/mL, the IVT vancomycin was held, and another CSF sample was obtained in 24 hours. Fluid was extracted from the shunt each day and sent to the laboratory for microbiological assessment. Once three consecutive negative CSF cultures were reported, the patient's shunt was replaced or revised, and IVT and IV vancomycin were continued for an additional two days.

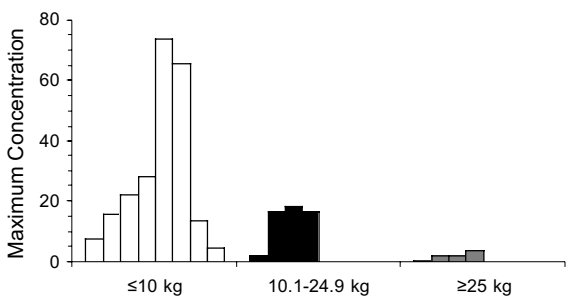
Patient demographic data including age, weight, gender, shunt type, and diagnosis requiring initial shunt placement were noted. Likewise, microbiological data, IVT/IV vancomycin doses, concomitant antibiotics, CSF and serum vancomycin concentrations, and CSF drainage output were recorded. Pearson correlation was used to assess the relationship between vancomycin CSF concentration and both age and CSF output. Statistical significance was set *a priori* at P ≤0.05, and all data are presented as mean±SD. Statistical analysis was performed using the MINITAB 13 statistical software (Release 13. Minitab, Inc.). The study was approved by the Institutional Review Boards of The University of Tennessee Health Science Center and Le Bonheur Children's Medical Center, and informed consent was deemed unnecessary.

RESULTS

Patient demographics are depicted in Table 1. Seventeen patients (10 females), mean age of 5.5±6.1 years (range: 4 months–17 years), weight of 23.6 ± 30.3 kg (range: 3.3–117 kg), were hospitalized for shunt infections. Sixteen patients had VP shunts, and the remaining one had a VA shunt. Underlying pathologies that required initial shunt placement varied; however, intraventricular hemorrhage, tumor, and spina bifida were the most predominant causes (Table 1). All patients had positive CSF cultures for *S. epidermidis* (n=12), *S. aureus* (n=3), *group B streptococci* (n=1) and *Bacillus species* (n=1) (Table1). Ninety-five percent of shunt catheters were externalized during IVT vancomycin therapy.

Sixteen patients received 10 mg/day of IVT vancomycin, while one patient (# 17) received 5 mg/day. The mean duration of IVT vancomycin therapy was 10.9±4.9 days but ranged from 3 to 23 days. The mean number of doses given during this time was 8.5±4.1 (range: 2–16). Trough CSF vancomycin concentrations were obtained prior to a dose in 17 patients across the duration of therapy and ranged from 0.4 to 187.3 μg/mL. If one excludes patient 17 whose vancomycin concentration was 187.3 μg/mL, the mean maximum CSF trough concentration was 18.4±21.8 μg/mL. All four adolescents ≥25 kg had CSF vancomycin concentrations ≤5 μg/mL (2±1.4; range:0.4–3.8 μg/mL), three of four infants/children between 10.1 and 24.9 kg had trough CSF vancomycin concentration between 10–20 μg/mL (13.5±7.7; range: 2–18.5–mg/L), and five of nine infants ≤10 kg had CSF vancomycin con-

Figure. Maximum CSF vancomycin concentration for each of the 17 patients.



Patient 17 not shown in this figure. Because the graph stops at 80 μg/mL, the actual concentration for patient 17 was 187.3 μg/mL.

centration >20 μg/mL (29.1± 26.3; range: 4.8–73.8 μg/mL) (Figure). Because patient 17 had an unusually high concentration (187.3μg/mL), which unduly influenced the ≤10 kg group, he was excluded from the above mean data. Daily CSF drainage outputs were available in fourteen patients and were averaged for the duration of their hospitalization (Table 2). Mean ± SD was 374.5 ± 246.23 mL/day (range: 44–1054 mL/day). Although there was a poor and non-statistically significant correlation between age (r^2=0.14; P=0.135) and maximum CSF trough concentration, there was a poor, but statistically significant correlation between CSF output and maximum CSF trough concentration (r^2=0.68; P=0.01). Hence, neither age nor CSF output could be used to predict trough CSF vancomycin concentration. These data are limited by the small sample size of our study.

Sixteen patients received concomitant IV vancomycin. Infants and children received a mean IV vancomycin dose of 54.6±9.1 mg/kg/day (range: 40–70 mg/kg/day), while adolescents received 2–3 g/day (Table 2). Eleven patients had trough serum vancomycin concentrations monitored, which ranged from 3.6 and 76.3 μg/mL. Patients 9 and 14 had elevated systemic vancomycin concentrations secondary to varying degrees of renal failure.

All organisms were successfully eradicated as evidenced by CSF cultures becoming sterile by a median of four days (range: 2–10 days). There were no complications from the administration of IVT vancomycin except for patient 17 who developed chronic CSF eosinophilia that was presumed related to a high CSF vancomycin concentration of 187.3 μg/mL.

Table 2. Treatment Outcomes

Pt	Days of IVT VAN (No. of doses)	CSF VAN-T Concentration* (Range)	Average CSF Output (mL/d)	IV VAN Dose† (days)	Serum VAN-T Concentration* (Range)	Concurrent Antibiotics	Negative CSF Culture (Days‡)
1	15 (9)	0.4§	259.2	2 g/day (21)	3.6	IPM	8
2	13 (13)	(1.1–2.0)	296.4	2 g/day (14)	8.7	NIT	7
3	11 (7)	1.9§	413.1	3 (1)	NA	AMP/GEN	4
4	6 (5)	2§	457.2	42 (3)	NA	CAZ	4
5	11 (9)	(1.2–3.8)	578.8	60 (10)	14.7	None	3
6	10 (9)	(0.5–4.8)	N/A	70 (5)	NA	CAZ	4
7	9 (9)	(0.6–16.7)	185	60 (3)	NA	None	6
8	13 (10)	(2.4–7.7)	283.3	48 (7)	6.2	NAF/RIF	3
9	23 (15)	(3.9–18.5)	467	60 (27)	(9.6–76.3)	CTX/TOB	4
10	16 (16)	(7.7–15.8)	N/A	60 (15)	6.5	None	10
11	10 (6)	(9.0–14)	272.2	60 (10)	10.7	CTX/FLG	4
12	10 (7)	22.1§	123.3	60 (16)	10.3	CTX	8
13	11 (7)	(43.8–65.8)	N/A	60 (5)	15.3	None	5
14	3 (2)	(54.8–73.8)	44	51 (14)	(4.2–54.8)	None	3
15	6 (4)	(5.6–16.7)	306	40 (5)	(10.8–12.9)	None	5
16	4 (3)	(9.9–28.4)	504	54 (7)	NA	GEN/FLG/CAZ	2
17	15 (14)	(1.0–187.3)	1054	40 (5)	NA	AMP/CTX/NAF	9

* = *mg/mL*
† = *all dose in mg/kg/d unless otherwise noted*
‡= *the first day the culture was negative on vancomycin*
§ = *patient only had one CSF vancomycin concentration drawn*

DISCUSSION

Ninety percent of organisms infecting CSF shunting devices are *Staphylococcus* and *Streptococcus species*.[17] Several series have reported that staphylococcal organisms (i.e., *S. epidermidis* or *S. aureus*) account for 50% to 60% of shunt infections, with the remainder being caused by *Streptococcus* species, *Cornebacterium* species, gram-negative bacillus, diptheroids, and micrococcus species. These numbers are consistent with the organism profile noted in our series of patients with 70.5% of infections caused by *S. epidermidis* and 17.6% caused by *S. aureus*.

Although these infections can be associated with significant morbidity and mortality, a standardized therapeutic approach has not been universally accepted. Empiric IVT vancomycin doses (i.e., 5, 10, 20 mg/day) have resulted in unpredictable CSF vancomycin trough concentrations. In our series, all patients except one received an IVT dose of 10 mg in conjunction with IV vancomycin. The 10 mg IVT dose is larger than that suggested by Gump, who advocates that the IVT vancomycin dose should not exceed 5 mg/day unless CSF concentrations are inadequate.[18] However, our doses are lower than the 20 mg/day dose in children and are equal to the 10 mg/day dose in newborns that McLaurin and colleagues recommended.[19] Based on results from a small series of patients, Pfausler et al. also recommended that a 10 mg IVT dose of vancomycin would achieve mean trough CSF vancomycin concentrations between 5–10 μg/mL in shunt-associated ventriculitis.[20]

The magnitude and range of vancomycin trough CSF concentrations following a 10 mg dose of IVT vancomycin was extremely variable in our study. Patients had resultant trough CSF vancomycin concentrations ranging from 0.4 to 187.3 μg/mL. The varibility is similar to that noted by Bayston et al. who reported that CSF vancomycin concentrations ranged from 5 to 236 μg/mL.[1] The mean maximum CSF concentration noted in our study was higher (18.4±21.8 μg/mL; range 0.4–187.3 μg/mL) than that noted by others.[19,20] Likewise, concentrations resulting from a 10 mg IVT dose were higher in infants than what was suggested by McLaurin.[19] Fifty-five percent of our infants ≤10 kg had a CSF trough vancomycin concentration >20 μg/mL. All four adolescents in our series ≥25 kg had CSF vancomycin concentrations ≤5 μg/mL. These finding are consistent with Bayston et al. who reported that larger doses (i.e., 20 mg/day) should be administered to adults based on larger ventricular size and volume.[1]

CNS volume of distribution (Vd) and clearance of vancomycin may be altered in patients with shunt infections. Normally, CSF is completely exchanged 3–4 times per day,[21] thereby influencing drug clearance from the CSF. In addition, most patients with ventriculitis whose shunts are externalized have abnormal CSF circulation. Likewise, diseases such as hydrocephalus and ventriculitis may also alter the dynamics of the CSF.[4] The majority of drug clearance occurs by bulk flow of CSF across the arachnoid villi.[22] Patients with ventriculitis may have decreased clearance of vancomycin secondary to a fall in CSF production.[23] A significant decrease in the rate of CSF formation has been reported using a rabbit model of acute ventriculitis.[24] In this model, CSF formation decreased by 48%–53% (culture-proven infection) and 56%–66% (clinical signs of infection) when compared to controls without CNS infection.

On the other hand, Haworth et al. noted that the clearance of vancomycin following a 3 mg dose was not significantly changed in rabbits with ventriculitis when compared to controls.[24] Conversely, rabbits that received a larger dose of vancomycin (120 mg) had slower elimination rates.[24] These findings imply that the CSF clearance of vancomycin may display a dose-dependent saturable characteristic. An 82-year-old male who received 50 mg IVT vancomycin was noted to have a stable Vd that reflected the physiologic CSF volume (0.25 L).[25] These authors also noted that the elimination half-life doubled after 24 hours of therapy (9.3 hours vs. 20.5 hours). Accumulation of vancomycin following IVT administration has also been reported by other investigators.[3,19,21]

Bayston et al. did not find any correlation between age and vancomycin CSF concentration.[1] Similar to Bayston et al., we did not find a significant correlation between age and CSF vancomycin trough concentrations. Based on retrospective data, Bayston and colleagues also suggested that the dose of IVT vancomycin should be based on ventricular volume.[1] They recommended that patients with ventricular size equal to or larger than those of an average adult be

given 20 mg/day of IVT vancomycin.[1] This is inconsistent with LeRoux who reported that ventricular volume did not correlate with CSF vancomycin concentrations.[26] Because our study was retrospective, we did not assess ventricular volume using MRI; however, we found no correlation between the daily output of CSF and CSF trough vancomycin concentrations

While there is no clear reference range for vancomycin in the CSF, several authors have suggested "desired concentrations" based on individual experiences and have attempted to associate this with a specific dose. Theoretically, CSF vancomycin concentration <5 μg/mL and >10 μg/mL are not warranted. This is supported by Nagal et al. who prospectively studied the bactericidal activity of vancomycin in CSF.[12] They examined the *invitro* activity of vancomycin at high concentrations against *S. aureus* and *S. epidermidis* in human CSF samples. They found equal efficacies for concentrations of 10, 100, and 300 μg/mL. A concentration of 5 μg/mL showed slightly lower activity, but this difference was not significant, whereas a concentration of 2 μg/mL was significantly less bactericidal. All patients in our study had microbiological and clinical cures. These cure rates are suprising because 35% of patients did not achieve CSF trough vancomycin concentrations >5 μg/mL. Although higher CSF vancomycin concentrations occurred over the dosing interval and may have been adequate to treat most CSF infections, it is the trough concentrations that have been monitored and associated with outcome.[12]

One patient in our study developed chronic eosinophilia in the CNS, which was assumed to be associated with an elevated CSF vancomycin concentration (187.3 mg/mL. Although other factors can contribute to CSF eosinophilia (e.g., the shunt as a foreign body), this side effect is consistent with two case reports previously described.[27] In order to reduce the potential for toxicity, Pau et al. adjusted vancomycin dosages to maintain CSF trough concentrations below 20 μg/mL.[3]

CONCLUSIONS

Although CSF trough vancomycin concentrations are highly variable following the administration of a 10 mg IVT dose of vancomycin, we recommend beginning with 10 mg/day of IVT vancomycin in conjunction with age-appropriate IV vancomycin dosing for CNS infections. The variability in CSF concentration after this dosage requires practitioners to monitor trough CSF vancomycin concentrations and calculate the pharmacokinetic parameters (e.g., volume of distribution, CSF elimination half-life) after initial dosing.[28] Our series of patients suggests that concentrations appear to be lower in older children (i.e., <5 μg/mL) and elevated in younger patients <10 kg (i.e., >20 μg/mL). This may require doses of 20 mg/day of IVT vancomycin in adolescents or in patients who are unresponsive to initial doses.[25,28] Likewise, if CSF trough concentrations are elevated in infants or in patients experiencing non-linear clearance from the CSF, doses of 5 mg/day may be indicated. Because dosing recommendations for IVT vancomycin are debatable and guidelines that reflect a CSF vancomycin dose-concentration relationship are unavailable, there is a need for well-designed prospective studies to determine the optimal therapy of IVT vancomycin that would insure success while avoiding toxicity.

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